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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/078,949 | 02/20/2002 | Stanley T. Crooke | ISIS-5027 | 8454 |

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COZEN O'CONNOR, P.C.
1900 MARKET STREET
PHILADELPHIA, PA 19103-3508

| EXAMINER | |
|---|---|
| MCGARRY, SEAN | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1635 | |

DATE MAILED: 02/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/078,949 | CROOKE, STANLEY T. | |
| | Examiner | Art Unit | |
| | Sean R McGarry | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *94-164* is/are pending in the application.

4a) Of the above claim(s) *112,114-120,127-156 and 159-164* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *94-111,113,121-126,157 and 158* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/23/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's election with traverse of Group I and the species "peptide nucleic acid" in the reply filed on 11/08/04 is acknowledged. The traversal is on the ground(s) that there is no serious search burden imposed on the examiner by combining several of the groups. This is not found persuasive because applicant has not provided evidence or specific arguments that would show any error in the reasons set forth for restriction in the Restriction requirement mailed 10/06/04.

The requirement is still deemed proper and is therefore made FINAL.

Claims 112, 114-120, and 127-154 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and claims 155, 156, and 159-164 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/08/04. It is noted that applicant asserts in the response filed 11/08/04 that claims 155-164 are all generic to the elected species, but claims 155, 156, and 159-164 recite species nonelected and are withdrawn.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 94-98, 100-102, 104-111, 113, 121, and 123-125 are rejected under 35 U.S.C. 102(b) as being anticipated by Agrawal [WO 94/01550].

Agrawal et al discloses self-stabilized oligonucleotides that are double stranded and comprise at least four RNA units and can contain modifications. (See Example 3, Example 5 and Figures 1-7, lines 5-23 of page 16, and the claims, for example). The self-stabilized oligonucleotides are contacted with mammalian cells for the inhibition of viral and cellular RNAs. The oligonucleotide (ribozymes) of Figure 7, for example is a double stranded RNA that may contain modifications and used to inhibit viral RNA in a cell. Ribozymes cleave targets. Furthermore, since the compounds used by Agrawal meet all of the structural limitations of the compound of the instantly claimed methods, the compounds of Agrawal would inherently act to modify a target RNA, activate dsRNAse in a cell and also modify the levels of a target RNA in a cell as in the claimed methods when used as disclosed by Agrawal. The cleavage products recited in the claims would be expected to be inherently produced by the methods of Agrawal, for example and would further be expected to activate the same dsRNase since the compounds for use in the methods of Agrawal meet all of the structural requirements of the compounds used in the instantly claimed methods.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 157 and 158 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal as applied to claims 94-98, 100-102, 104-111, 113, 121, and 123-125 above, and further in view of Hunziker and Leumann, Nucleic Acid Analogues: Synthesis and Properties in Modern Synthetic Methods 1995, ed. Ernst and Leumann, pages 331-417, 1995.

The difference between the Agrawal reference and the instant invention is the inclusion of peptide nucleic acid modifications. It is noted that further to what is described above for Agrawal, the following is also relied upon: At page 16 it is taught "The self-complementary region may contain ribonucleotides, deoxyribonucleotides, analogs of ribonucleotides or deoxyribonucleotides having artificial linkages, or combinations of the above. The ability to activate RNase H is not important for the self-complementary region, so nucleotides having artificial linkages that do not activate RNase H can be used without diminishing the effectiveness of the oligonucleotide." It is clear from the Agrawal reference that modifications are clearly contemplated for use in the invention. Agrawal does not specifically teach the use of peptide nucleic acid modifications.

However, Hunziker and Leumann teach, at page 381, teach the benefits of PNA modifications and assert that the bioavailability and biostability of PNA are of special interest to antisense and antigene applications.

One of ordinary skill, apprised of the teachings of the prior art would clearly contemplate the use of PNA modifications in the self stabilized oligonucleotides of Agrawal since Agrawal clearly teach the use of modifications to oligonucleotides in antisense applications and since Hunziker and Leumann have taught that PNA modifications are of special interest in antisense applications.

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 94-103, 105-111, 123, 125, 126, 157 and 158 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant points to pages 6-8, 9-14, 17, 18, 20, 21, 24, 27, 30, 91, 92, and 94-96, Figure 4 and Claim 1 as originally filed for support for new claims 94-154, filed as a preliminary amendment with the application. Applicant points to pages 4, 6-14, 17, 18, 20-27, 30, 32, 91, 92, and 94-96, Figure 4, and claim 1 as originally filed for support for

new claims 155-164 filed 4/11/02. Applicant provides no specific direction were support can be found for any particular claim or limitations introduced in the preliminary amendments. Applicant is directed to MPEP 714.02(c) and the examiner requests that applicant provide particular support for any additional new claims or amendments that may be filed in response to the instant Official Action. Furthermore, no support could be found from applicants general pointing of support for the indicated new matter and such support was not readily apparent from the application or claims as originally filed. If applicant believes that there is support for the indicated new matter, applicant is requested to point to such support with particularity since the applicant is far more apprised of the support from their drafting of the claims and/or amendments.

The above claims all contain new matter. Claims 94-103, 105-111, 123, 125, 126, 157 and 158 are all drawn to methods of modifying a target RNA, activating a nuclease within a cell, or modulating the levels of a target RNA via the contacting of a cell with a **double stranded RNA** that contains a modification. The specification is drawn to "oligomeric compounds formed from a linear sequenceof linked ribonuceoside units that are specifically hybridizable to a preselected RNA target. "(See page 6 of the instant specification). Furthermore, the specification discusses the properties of single stranded RNA or RNA-like oligomeric compounds that **form double strands with a target RNA** and are cleaved by a specific dsRNase (see page page 16, lines 22-29, for example). The examiner was at a loss to find any support for a double stranded compound was contacted with a target RNA for modification or modulation.

It is noted that pages 90-94 describe the use of specific double stranded chemically modified sense and antisense oligonucleotides in an assay to detect dsRNase activity in cellular extracts. However there was no support found in the specification or claims as originally filed for any methods of activating a nuclease activity within a cell with double stranded RNA. The purpose of the examples was to isolate RNase activity from cellular exatracts and it is unclear how this might be extrapolated to provide support for activating dsRNase in a cell.

Claims 95 and 106 recite "first and second strands [of the double sstranded RNA] are covalently bound together." No support was found for this limitation and no specific support was provided.

Claims 96 and 107 recite "wherein the first and second strands form a single strand of RNA." No support was found for this limitation and no specific support was provided.

Claim 101 recites "the target RNA is present in the cytoplasm of the cell". No support was found for this limitation and no specific support was provided.

Claim 102 recites ""wherein the target RNA is present in the nucleus of the cell". No support was found for this limitation and no specific support was provided.

Claim 103 recites "wherein the target RNA is present in the mitochondria of the cell" No support was found for this limitation and no specific support was provided.

Claims 157 and 158 recite "at least one peptide nucleic acid". At page 20, lines 27-29, it appears that the specification requires that there be plural number of peptide nucleic acid segments. The specification appears to only refer to peptide nucleic acid

segments. No support for "at least one peptide nucleic acid" was found and no specific support was provided.

Claims 157 and 158 recite "contacting the target RNA with a compound comprising at least four consecutive. . ." and "contacting the target RNA with a double stranded compound comprising at least four consecutive. . .". It is noted that support could only be found for "oligomeric compounds" in the specification and claims as originally filed. No support could be found, for example for anything other than oligomeric compounds. The new limitations appear to broaden the scope to a range not disclosed or described in the application as filed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sean R McGarry
Primary Examiner
Art Unit 1635

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